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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,713	06/29/2001	David H. Sachs	59056-131CON	7385

23483 7590 10/03/2002

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/03/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/895,713	SACHS, DAVID H.	
	Examiner	Art Unit	
	Anne M Wehbé	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-39 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's pre-amendment received 2/1/02 has been entered. Claims 1-21 have been canceled and new claims 22-39 have been entered. Claims 22-39 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention as claimed. The specification discloses recipient bone marrow hematopoietic stem cells comprising a heterologous DNA which encodes a donor allogeneic MHC class I or class II antigen, and methods of inhibiting immune responses against donor allogeneic tissue by pre-administering said recipient cells to a recipient prior to allotransplantation. In regards to the composition claims 22-

33, it is noted that the specification teaches that the intended use for these cells is the induction of allogeneic transplantation tolerance by re-introducing said stem cells back into the host wherein the recombinant stem cells induce tolerance to a tissue from an allogeneic donor which expresses the same MHC antigen expressed by the stem cells. The specification does not provide an alternate use for the disclosed cells other than their use in preventing transplant rejection.

The specification does not provide an enabling disclosure for the induction of tolerance to allogeneic tissue comprising re-introducing hematopoietic stem cells from a recipient which have been modified to express an allogeneic MHC class I antigen into said recipient animal prior to transplantation of tissue from an allogeneic donor which expresses the MHC class I molecule as the modified recipient cells. The art at the time of filing teaches that donor-specific tolerance to allogeneic tissue is a crucial issue in transplantation. Without potent immunosuppressive therapy, foreign tissue is rapidly rejected by the host mammal's immune system. Rejection is mediated by cytotoxic CD8 +T cells, CD4+ T cells, NK cells, and antibody-dependent cellular cytotoxicity. (Kaufman et al. (1995) Annu. Rev. Immunol., Vol. 13, pages 342-343; Sablinski et al. (1997) Surgery, Vol. 121, page 382, paragraph 2; D.H. Sachs (1993) Ann. Thorac. Surg. , Vol. 56, page 1226 column 1, paragraph 2). In particular, cytokines secreted from allo-activated CD4+ and CD8+T cells mediate inflammatory destruction of graft tissue. Thus, prevention of rejection in allotransplantation requires inhibition or suppression of multiple components of both the immune and inflammatory responses.

In view of the complexity of the immune response to allogeneic tissue as discussed above, the specification does not provide sufficient guidance for inducing tolerance to a donor allograft by re-introducing recipient cells which have been transduced to express a single allogeneic MHC class I allele prior to the transplantation of allogeneic tissue which also expresses the allogeneic MHC class I allele. The specification's working examples utilize two congenic strains of mice which are genetically identical except for a single MHC class I disparity. The examples demonstrates the transduction of hematopoietic stem cells from the first strain with a retrovirus encoding the disparate MHC class I allele (K^b), and the administration of these cells to lethally irradiated mice of the first strain followed by transplantation of skin from the congenic mouse strain resulting in prolongation of graft survival compared to control mice. Unlike the applicant's congenic model system, allogeneic transplantation involves multiple MHC class I and class II disparities, not to mention minor histocompatibility differences. The applicant's working examples do not demonstrate that a single class I allele can tolerize the spectrum of T cells which recognize all the different MHC antigens expressed by the donor mammal. As T cell tolerance, like T cell activation, is an antigen specific event, the skilled artisan would not have had a reasonable expectation that a single MHC class I allele could tolerize T cells which recognize epitopes from other class I or class II alleles. Further, at the time of filing, it was well known that in the absence of immunosuppressive therapy, even a single MHC mismatch can result in rejection of the transplanted tissue. Thus, based on the unpredictability of inducing tolerance to allotransplants as taught by the art at the time of filing, the lack of guidance provided by the specification for

overcoming T cell and NK cell mediated rejection of multiple MHC class I and class II disparities in transplanted allogeneic tissue, the insufficiency of the provided working examples, and the breadth of the claims, the skilled artisan would not have predicted success in using the recombinant hematopoietic stem cells of the instant invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 recites the limitation "said mammal" in claim 28. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22, 23, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. (1989) Transpl. Proc., Vol. 21 (1), 477 in view of Pullen et al. (1986) J. Immunol., Vol. 137, 1359-1365. The applicant claims mammalian bone marrow hematopoietic stem cells comprising DNA encoding an MHC class I antigen from an MHC nonidentical donor of the same species.

Madsen et al. teaches H-2^k murine L cells transfected with either class I or class II genes from a H-2^b mouse (Madsen et al., page 477, column 1, paragraph 2). In addition, Madsen et al. provides motivation for transfecting cells with either class I or class II genes of a different haplotype by teaching that the presence of either a non-identical MHC class I or class II gene on cells or tissues prolongs the survival of organ grafts of the same haplotype as the transfected MHC gene in animals (Madsen et al., page 477, column 2, paragraph 2).

Madsen et al. does not teach the transfection of hematopoietic stem cells with either MHC class I or class II.. Pullen et al. supplements Madsen et al. by teaching the transfection of murine H-2^b bone marrow, which contains hematopoietic stem cells, with the murine MHC class II Eα^d gene, which represents a different haplotype from the MHC of the H-2^b mouse (Pullen et al., page 1359, abstract, and pages 1359-1360, bridging paragraph). Further, Pullen et al. provides motivation for transfecting bone marrow stem cells by teaching that bone marrow is an excellent population of cells for genetic manipulation because these cells can be extracted from an animal, grown in culture, and then successfully reimplanted into the animal (Pullen et al., page 1359, column 2, paragraph 4). Thus, based on the motivation to use bone marrow stem cells for genetic

manipulation provided by Pullen et al., and the motivation to transfect cells with MHC class I or II genes of a different haplotype provided by Madsen et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to transfect bone marrow hematopoietic stem cells with genes for MHC class I of a different haplotype using the well-known techniques taught by Madsen and Pullen. Furthermore, based on the successful expression of MHC in transfected bone marrow observed by Pullen et al., the skilled artisan would have had a reasonable expectation of success in transfecting bone marrow stem cells with a vector encoding an MHC class I molecule of a different haplotype.

Please note that in regards to the functional language of claim 23 regarding immune inhibition following introduction of the cells into a recipient, the MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Claims 24-27 and 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. (1989) Transpl. Proc., Vol. 21 (1), 477 in view of Pullen et al. (1986) J. Immunol., Vol. 137, 1359-1365, as applied to claims 22, 23, and 28 above, and further in view of Bernstein et al. (1986) Cold Spring Harbor Symp. on Quant. Biol., Vol. LI, 1083-1091. The applicant claims mammalian bone marrow hematopoietic stem cells comprising DNA encoding an MHC

class I antigen from an MHC nonidentical donor of the same species, wherein the DNA is introduced into said cells by transduction with a retroviral vector, specifically a Moloney-based retroviral vector, or wherein the cells are human.

As discussed above, Madsen et al. teaches H-2^k murine L cells transfected with either class I or class II genes from a H-2^b mouse and motivation for transfecting cells with either class I or class II genes of a different haplotype in order to prolong the survival of organ grafts of the same haplotype as the transfected MHC gene in animals (Madsen et al., *supra*). Pullen et al. was cited as supplementing Madsen et al. by teaching the transfection of murine H-2^b bone marrow, which contains hematopoietic stem cells, with the murine MHC class II Eα^d gene (Pullen et al., *supra*). Further, Pullen et al. provides motivation for transfecting bone marrow stem cells by teaching that bone marrow is an excellent population of cells for genetic manipulation because these cells can be extracted from an animal, grown in culture, and then successfully reimplanted into the animal.

Neither Madsen nor Pullen specifically teach the use of a retrovirus or Moloney-based retrovirus to introduce an MHC gene into cells, or the transfection of MHC genes into human cells. Bernstein et al. supplements Madsen et al. and Pullen et al. by teaching that retroviral vectors, particularly Moloney-based retroviral vectors, can be used to introduce DNA into murine or human hematopoietic stem cells in culture (Bernstein et al., page 1084, Figure 1, page 1084-1085, bridging paragraph, and page 1085, column 1). In addition, Bernstein et al. provides motivation for using retroviral vectors rather than other vectors known at the time of filing by teaching that the low frequency of stem cells in the hematopoietic system necessitates the use of

highly efficient gene transfer techniques, and that retroviruses are ideally suited as gene transfer vectors due to their high infection efficiency, stable integration into the host genome, and high level of gene expression (Bernstein et al., page 1083, column 1, paragraph 2). Thus, based on the unique features of retroviruses taught by Bernstein et al., and the benefits of transfecting MHC genes into bone marrow stem cells taught by Pullen et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute a retroviral vector for the cosmid or plasmid vectors taught by Madsen and Pullen et al. in order to more efficiently and stably transduce bone marrow stem cells. Further, the artisan would have had a reasonable expectation of success in expressing an MHC class I gene in murine or human hematopoietic stem cells based on the successful use of retroviruses to express heterologous genes in stem cells taught by Bernstein et al.

As noted above in regards to the functional language of certain claims regarding immune inhibition following introduction of the cells into a recipient, the MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER